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EXAMINER	
BRISTOL, LYNN ANNE	

ART UNIT	PAPER NUMBER
1643	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/528,073	VALKNA ET AL.	
	Examiner	Art Unit	
	LYNN BRISTOL	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE _3_ MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on _21 November 2008_.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) _19-23 and 26-33_ is/are pending in the application.

4a) Of the above claim(s) _27-30_ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) _19-23,26 and 31-33_ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)

2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _11/21/08_.

4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.

5) ☐ Notice of Informal Patent Application

6) ☐ Other: _____.

DETAILED ACTION

1. Claims 19-23 and 26-33 are all the pending claims for this application.

2. Claims 19-23 and 26 were amended, and new Claims 31-33 were added in the Response of 11/21/08.

3. Claims 27-30 are withdrawn from further consideration pursuant to 37 CFR 1.142(b).

4. Claims 19-23, 26 and 31-33 are all the pending claims under examination.

5. This Office Action contains new grounds for rejection.

Information Disclosure Statement

6. The references filed in the IDS of 11/21/08 have been considered. The copy of the examiner's initialed 1449 form is attached.

Application Disclosure Statement

7. The replacement Application Data Sheet filed 11/21/08 is in compliance under MPEP 601.05 or 37 CFR 1.76.

Withdrawal of Objections

Specification

8. The objections to the specification are withdrawn for the following reasons:

a) the peptide sequences of $\geq$4 amino acids in length (see p. 9, line 15: (Gly4Ser)3) have been amended to recite a sequence identifier pursuant to 37 CFR 1.821-1.825;

b) the objection to the legend to Figure 3 for reciting "recombinant protein" is withdrawn in view of the amended specification.

Withdrawal of Rejections

Claim Rejections - 35 USC § 112, second paragraph

9. The rejection of Claim 22 for the recitation "wherein the scFv-part is derived from the human genome" is withdrawn in view of the amended claim.

Rejections Maintained

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement

10. The rejection of Claims 23 and 26 under 35 U.S.C. 112, first paragraph is maintained because the specification does not reasonably provide enablement for a therapeutic use of the fusion protein in any subject in vivo for any disease including cancer much less where the subject is a human.

For purposes of review, the rejection was set forth in the Office Action of 5/21/08 as follows:

"<u>Nature of the invention/ Skill in the Art</u>

The claims are interpreted as follows: Claim 23 is drawn to any fusion protein comprising at least any scFv-part of any antibody and any cell penetrating transport peptide (CPP) of Claim 19 with the fusion protein having any medical use. Claim 26 is drawn to a pharmaceutical composition comprising at least one fusion protein of Claim 19 in association with at least one pharmaceutically acceptable carrier or additive.

The relative skill in the art required to practice the invention is a clinical diagnostician with a background in antibody-based methods.

<u>Disclosure in the Specification</u>

The specification teaches in general that cancer-specific antibodies to cancer-specific intracellular signals can be used for treatment of diseases by modulating the uptake of the antibodies into disease-affected cells in order to inactivate the intracellular targets (p. 2, lines 17). The specification teaches that "delivery of the scFv intrabodies remains a problematic issue for their potential therapeutic applications (p. 3, lines13-14). To solve this problem, the specification teaches peptide-mediated membrane penetration to deliver antibodies or scFvs to intracellular target proteins (p. 3, lines 17-20). The specification describes the fusion proteins for use in the treatment of a disease or health disorder in "humans or animals" (p. 5, lines 1-2). The specification describes cell penetrating peptides (CPPs) such as transportan for transporting antibodies into cells (p. 4, lines 3-4).

Working examples in the specification are the following:

Example 3 (working): describes conjugating CPP (transportan 10) to polyclonal antibodies for GLI1 and GLI3. The anti-GLI1-CPP conjugate is described as being shown in Figure 2 to be taken up after 3 and 14 hour incubations by Cos-1 cells compared to unconjugated GLI-1.

Example 7 (working): describes making a fusion protein from the cloned VH and VL domains of the anti-GLI-1 or GLI-3 antibody and being linked with a linker where the CPP (9Arg or Transportan or Transportan 10) is interposed between the VL and linker portion of the molecule (e.g., VL-TP-linker-VH). The specification teaches that the antibodies bind to the GL1 protein and also entered eukaryotic cells in culture. <u>***If***</u> the data in Figure 3 correspond to this example, then it appears the anti-GLI1 scfv-TP embodiment is taken up into human 293 cells in vitro.

The specification is insufficient and therefore non-enabling in its disclosure for using any fusion protein comprising any scfv fused to any CPP in any medical use or any pharmaceutical application, because of the limited number of working embodiments which are shown to a) have uptake or increased uptake by cells by virtue of the CPP, and more importantly, b) that the internalized fusion protein retains specific antigen binding, yet would still have an inactivating effect on the target antigen through the scfv. The specification has not provided a single working example of any fusion protein demonstrating all of these properties, therefore, because the ordinary artisan could not predict which combination of scfv and CPP could be used together to impart to a fusion protein all of the preceding properties, the ordinary artisan would be required to perform undue trial and error experimentation in order to practice the invention as claimed. The specification is even less enabling for using the fusion protein in vivo to treat any disorder in any subject much less where the subject is a human. The specification is not enabling for using the fusion protein to treat any cancer in vitro or in vivo. The specification provides an enabling disclosure for using the fusion protein to identify intracellular target antigens, which might otherwise be difficult to detect with a scfv absent the CPP

moiety, and which could have applications for in vitro diagnostics. Otherwise, one of skill in the art could not deduce from the specification which of the myriad combinations of scfv and CPP encompassed by the claims and the myriad medical uses especially where the intended medical use was treating any cancer, would be effective in humans or animals.

Prior Art Status: Translation of Therapeutics from In vitro to In vivo is Unpredictable

The claims encompass using the fusion protein in any medical application or impliedly in unlimited pharmaceutical applications. The specification explicitly contemplates using the fusion protein for cancer therapy in animals and humans.

A tumor is a 3-dimensional complex consisting of interacting malignant and non-malignant cells. Vascularisation, perfusion and drug access to the tumor cells are not evenly distributed and this is an important source of heterogeneity in tumor response to drugs. Therefore, prediction of drug effects in any animal model or even a human based solely on a single in vitro experiment as in the present case is not reliable and further evaluation in animal disease model systems is essential.

Further, inasmuch as in vitro drug testing *may be* a platform technology in a determination of enablement, the complexity and difficulty of antibody delivery for cancer treatment is underscored by Voskoglou-Nomikos (Clin. Can. Res. 9:4227-4239 (2003)). Voskoglou-Nomikos conducted a study using the Medline and Cancerlit databases as source material in comparing the clinical predictive value of three pre-clinical laboratory cancer models: the in vitro human cell line (Figure 1); the mouse allograft model; and the human xenograft model (Figures 2 and 3). Significantly when each of the cancer models was analyzed against Phase II activity, there was a negative correlation for the in vitro human cell line models being predictive of good clinical value. No significant correlations between preclinical and clinical activity were observed for any of the relationships examined for the murine allograft model. And the human xenograft model showed good tumor-specific predictive value for NSCLC and ovarian cancers when panels of xenografts were used, but failed to predict clinical performance for breast and colon cancers. Voskoglou-Nomikos suggests that “the existing cancer models and parameters of activity in both the preclinical and clinical settings may have to be redesigned to fit the mode of action of novel cytostatic, antimetastatic, antiangiogenisis or immune-response modulating agents” and “New endpoints of preclinical activity are contemplated such as the demonstration that a new molecule truly hits the intended molecular target” (p.4237, Col. 1, ¶6).

Dennis (Nature 442:739-741 (2006)) also recognizes that human cancer xenograft mouse models for testing new drugs has been and will remain the industry standard or model of choice, but it is not without problems because “many more [drugs] that show positive results in mice have little or no effect in humans” (p. 740, Col. 1, ¶3). Dennis describes transgenic animal mouse models as an alternative to xenograft modeling and the general differences between mice and humans when it comes to tumor modeling: 1) cancers tend to form in different types of tissue, 2) tumors have fewer chromosomal abnormalities, 3) ends of chromosomes (telomeres) are longer, 4) telomere repairing enzyme active in cells, 5) short lifespan, 6) fewer cell divisions (10^{11}) during life than humans (10^{16}), 7) metabolic rate seven time higher than humans, and 8) lab mice are highly inbred and genetically similar.

Cespdes et al. (Clin. Transl. Oncol. 8(5):318-329 (2006)) review the some of the examples of art-recognized animal disease model correlates for the corresponding human disease in Tables 1-3. Cespedes emphasizes the challenges in using animal models as predictive correlates for human responsiveness to therapeutics and sets forth on pp. 318-319 a list of criteria that would represent the ideal in vivo model for studying cancer therapeutics. As regards the use of xenograft modeling, Cespedes teaches:

> "One limitation of the xenograft models is precisely their use of an immunocompromised host, which eliminates the possibility of studying the role of the immune system in tumor progression. Some authors also think that cancer and host cells being from different species may limit the occurrence of critical tumor-stroma interactions, leading to an inefficient signaling. The organ of implantation could also become a limitation to the system. Thus, as it has already been described, subcutaneous xenografts infrequently metastasize and are unable to predict response to drugs” (p. 325, Col. 1, ¶2).

At least for the HIV TAT peptide conjugate to the scfv for ED-B domain of fibronectin (Niesner et al., Bioconjug. Chem. 13(4): 729-736 (Jul-Aug 2002); Abstract), Niesner teaches that tumor targeting in vivo was severely reduced compared to the unconjugated antibody. Niesner teaches that the poor biodistribution of TAT-antibody conjugates casts doubt on the applicability of the method for delivery in vivo.

One skilled in the art based on the prior art teachings and the insufficiency of enabling data in the specification, would reasonably conclude that evidence obtained from a limited number of in vitro cell assays would not even necessarily correlate with results expected in any animal model much less a human subject.

Unpredictability/ Undue Experimentation

Given the unpredictability of translational experimentation for drugs and antibodies from in vitro cell-based assays to animal models much less to human trials and the insufficient experimental data provided in the specification, the ordinary artisan would be forced into undue experimentation to practice using the fusion protein for

any medical condition or for any pharmaceutical application especially where an intended therapeutic effect was to be observed in vivo."

Applicants' allegations on pp. 11-12 of the response of 11/21/08 have been considered and are not found persuasive. Applicants allege "It is well known that Gli is rapidly destroyed by the proteasome and that basal cell carcinoma induction correlates with Gli protein accumulation; Muller et al. (Drug Discovery Today, 4:285-291 (2007); cited in the IDS of 11/21/08) teaches anticancer drugs and correlate these targets with Gli proteins; and Applicants submit data comparing TP10, PBS anti-Gli1 ab, scantiGLi-TP10, scanti-Gli and cyclopamin on tumor volume for the PC3 xenograft tumor in nude mice (see bar graph on p. 12 of the Response). For these new data, Applicants allege the construct is more effective than cyclopamine alone.

Response to Arguments

The examiner has considered the full content of the Muller reference and finds the only meaningful disclosure for GLI inhibitors in cancer therapy at p. 290, Col. 2:

> "In this respect, converging evidences indicate that Gli transcriptional regulators (Hh pathway, figure 1) participate in many human maligancies and in the stemness signature of cancer cells. Chemical inhibitors of Gli-mediated transcription have been recently screened from libraries of organic compounds. Two compounds able to act in the nucleus to block Gli function have been isolated. One of them interfered with Gli1 DNA binding in living cells. The discovered compounds efficiently inhibited in vitro tumor cell proliferation in a Gli-dependent manner and successfully

blocked cell growth in an in vivo xenograft model using human prostate cancer cells harboring downstream activation of the Hh pathway [34]."

The reference [34] (Lauth et al. (PNAS 104:8855-8860 (2007)); cited in the PTO 892 form) cited in Muller describes small molecule drug inhibitors for GLI designed to block the final step of the Hh pathway. Lauth demonstrates this inhibitory effect for two (2) compounds (GANT 61 and GANT68) using in vitro cell-based assays and a human prostate cancer (22Rv1) xenograft model in mice (Figure 5), where tumor growth (volume) in the presence of GANT61 was minimal. Notably, the compounds of Lauth as incorporated by reference in Muller bare no relationship in their functional or structural features to the inventive recombinant fusion protein. Because of the general unpredictability of immunotherapy in cancer treatment as discussed in the previous Office Action, and in view of the non-analogous nature of the small molecule compounds to the fusion protein in treating cancer in vivo, Muller is not considered to provide further enabling disclosure for treating a human prostate cancer with an antibody-based fusion protein.

Still further, the extrinsic data on p. 12 of the Response showing a single in vivo experiment is enabling for an in vivo use of the inventive construct for demonstrating tumor inhibition (vis-à-vis change in tumor weight) for the human prostate cancer cell line, PC3, of approximately 50% compared to the controls. However, the submission of these new data as a new figure within the actual Response absent any attestation to the facts by the actual inventors is not compliant under 37 CFR 1.132. 37 CFR 1.132 states in part: "when any claim for an application is rejected to…, any evidence submitted to

traverse the rejection…on a basis not otherwise provided for must be by way of an oath or declaration under this section." The purpose of an a 1.132 declaration is to provide a means for submitting evidence to overcome a rejection, and the kind of evidence in the instant case does not fall under an exception.

Additionally, the examiner wishes to point out that Applicants did not contemplate using the inventive construct to treat a prostate cancer much less even a human prostate cancer cell line, e.g., PC3, in the original specification. Applicants are invited to identify written description support for prostate cancer or a prostate cancer cell lines in the specification and/or its priority documents. In the event the claims were amended to recite a prostate cancer, this would raise a new matter issue under 35 USC 112, first paragraph and 35 U.S.C. 132. Otherwise, Applicants could file a C-I-P application containing these new data, and any claims directed to treating a prostate cancer would obtain benefit of the filing date for the C-I-P for purposes of applying prior art (MPEP 2133.01).

The rejection is maintained for the reasons of record and as set forth herewith.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. The rejection of Claims 19, 22, 23 and 26 under 35 U.S.C. 102(b) as being anticipated by Zhao et al. (J. Method. Immunol. 254:137-145 (2001); cited in the PTO 892 form of 2/12/08) as evidenced by Pavlinkova et al. (J. Immunol. Methods 201:77-88 (1997)) is maintained.

For purposes of review, the rejection was set forth in the Office Action of 5/21/08 as follows:

> “Zhao discloses cross-linking an MTS peptide (membrane translocating sequence) derived from the signal region of Kaposi fibroblast growth factor to the 5D10 monoclonal antibody in order to render the antibody cell-permeable for live cells in vitro (e.g., Figure 4), where the complex is diluted in PBS and administered to cells in vitro. This is interpreted as reading on a pharmaceutical composition. The complex allows visualization of intracellular antigens for diagnostic purposes. Zhao teaches that the approach of linking an MTS can be performed on any antibody (p. 144, Col. 2, last line). Zhao teaches thru incorporation by reference to Pavlinkova that small peptides can be introduced into scfv antibodies, providing as indirect support, the manipulation of scfvs for modification to include MTS peptides and to enhance Fv uptake into cells.”

Applicants’ allegations on pp. 13-14 of the Response of 11/21/08 have been considered and are not found persuasive. Applicants allege the amendment to recite “recombinant fusion protein” in view of the definition of a “fusion protein” on the bottom of p. 13 of the Response in view of Zhao teaching protein conjugation by chemical or physicochemical linkage renders the rejection moot.

<u>Response to Arguments</u>

The skilled artisan would recognize that a scFv is itself a recombinant protein generated by recombinant technology from a parent antibody (see p. 3, lines 2-10 and pp. 8-9 of the specification). Additionally, cell membrane penetrating peptides, transportan and transportan 10, are both art-recognized chimeric or recombinant fusion peptides. For transportan, Lindgren et al (Trends in Pharm. Sciences 21:99-103 (3/2000); cited in the PTO 892 form of 2/12/08) at p. 101, Col. 1, ¶4 teaches:

"Galparan, a fusion between the neuropeptide galanin-l-13 and the wasp venom peptide mastoparan, was developed under a program that was aimed at creating galanin receptor antagonists by using a chimerical strategy. Because it was known that analogues with a substitution of Pro 13 to N^{ε}-biotinyl-Lys retained affinity for the galanin receptor, a similar substitution of Pro 13 was made on galparan. Strikingly, although cells incubated with labelled galanin showed almost no intracellular labelling, those incubated with the biotinylated galparan analogue were heavily labelled in both the cytoplasm and the nucleus. Thus, the new peptide was named transportan (Table 2)."

For transportan 10, Smoots et al. (Biochem. Biophys. Acta 1467:165-176 (2000); cited in the IDS of 11/21/08) teaches generating peptide mutants based on the wild-type chimeric transportan to generate transportan 10 as shown in Table I on p. 691.

The claims do not distinguish which portion of the fusion protein is recombinant. The claims do not distinguish the recombinant scfv portion of the protein being conjugated or recombinant fused to a cell penetrating transport peptide. The claims do not distinguish a recombinant scFv antibody being chemically linked or recombinant fused with a recombinant cell penetrating peptide like transportan or transportan 10, for example. Accordingly, Zhao as evidenced by Pavlinkova (see p. 144, Col. 2, line 21 to p. 145, Col. 1, line 6) teaches a recombinant fusion protein comprising a recombinant scFv antibody and a cell penetrating transport peptide associated with (conjugated to) the scFv antibody, which anticipates the claims.

12. The rejection of Claims 19, 21-23, 26 and 33 under 35 U.S.C. 102(b) as being anticipated by Rothbard (WO 98/52614; cited in the PTO 892 form of 2/12/08) is maintained.

For purposes of review, the rejection was set forth in the Office Action of 5/21/08 as follows:

> “Rothbard teaches poly -Arg peptides of from 4-9 residues (p. 7) or from 6 to 25 subunits (p. 10) for use as cell membrane transport peptides of selected agents across any number of biological membranes (p. 6, lines 1-7). Rothbard explicitly teaches delivering antibodies or antibody fragments such as scfv to the cytosol by attaching the transport polymers to the scfv, and that “the principle obstacle to wide application of this technology has been efficiency of uptake into infected cells” (p. 25, lines 10-21). Rothbard explicitly teaches fusion polypeptides comprising the polypeptide of interest and the transport peptide (p. 15, lines 15-20; p. 25, lines 29-31). Rothbard teaches that targets can be visualized with the fusion proteins (Example 4) and using the fusion proteins in pharmaceutical compositions (p. 7, lines 9-12).”

Applicants’ allegations on p. 14 of the response of 11/21/08 have been considered and are not found persuasive. Applicants allege “Rothbard et al. reference, Example no 4 teach Arg peptides that are conjugated with a fluorescent marker. However, the present claims encompass a recombinant fusion protein comprising at least (a) a scFv-part of an antibody, and (b) a cell penetrating transport peptide. Claim 21 is further distinguished in that this claim recites that the cell penetrating transport peptide is comprised of at least a part of Transportan, Transportan 10 or Arg 9. Rothbard et al. do not teach said protein either in conjugation or fusion with Arg peptides."

<u>Response to Arguments</u>

Rothbard teaches on p. 13, lines 15-20:

“B. <u>Fusion Polypeptides</u>

Transport peptide polymers of the invention can be attached to biologically active polypeptide agents by recombinant means by constructing vectors for fusion proteins comprising the polypeptide of interest and the transport peptide, according to methods well known in the art. Generally, the transport peptide component will be attached at the

C-terminus or N-terminus of the polypeptide of interest, optionally via a short peptide linker”,

which when taken in view of Rothbards further disclosure for scFv and cell membrane transport peptides, is considered to read on and therefore anticipate at least generic claim 19.

As regards Claim 21 for reciting “at least a part of”, the examiner submits Rothbard teaches subunit ranges for polyarginine peptides, which is considered to represent “at least a part of Arg 9.”

The rejection is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

13. The rejection of Claims 19, 20, 22, 23 and 26 under 35 U.S.C. 103(a) as being unpatentable over Zhao et al. (J. Method. Immunol. 254:137-145 (2001); cited in the PTO 892 form of 2/12/08) as evidenced by Pavlinkova et al. (J. Immunol. Methods 201:77-88 (1997)) in view of Toftgard (WO 01/12655; cited in the PTO 892 form of 2/12/08) is maintained.

For purposes of review, the rejection was set forth in the Office Action of 5/21/08 as follows:

"The claimed fusion proteins were prime facie obvious at the time of the invention over Zhao as evidenced by Pavlinkova in view of Toftgard.

Zhao discloses cross-linking an MTS peptide (membrane translocating sequence) derived from the signal region of Kaposi fibroblast growth factor to the 5D10 monoclonal antibody in order to render the antibody cell- permeable for live cells in vitro (e.g., Figure 4), where the complex is diluted in PBS and administered to cells in vitro. This is interpreted as reading on a pharmaceutical composition. The complex allows visualization of intracellular antigens for diagnostic purposes. Zhao teaches that the approach of linking an MST can be performed on any antibody (p. 144, Col. 2, last line). Zhao teaches thru incorporation by reference to Pavlinkova that small peptides can be introduced into scfv antibodies, providing as indirect support, the modification of scfvs to include cell membrane transport peptides. Zhao appreciates introducing cell membrane penetrating peptides into unlimited antibodies including scfvs as further evidenced by Pavlinkova, but does not teach scfvs for the family of GLI proteins for GLI-1 or GLI-3, whereas does Toftgard.

Toftgard discloses the GLI-1 protein (see entire document) and the GLI-3 protein (pp. 3, 24 and 36) and making antibodies against these intracellular antigens (p. 12, lines 1-14). Included amongst the antibodies are single chain antibodies and pharmaceutical compositions comprising the antibodies and carriers (p. 3, line 25; p. 12, lines 16-20; p. 13, lines 10-15). Toftgard teaches the technology for making protein fusion constructs in general (p. 28, lines 15-16).

One of ordinary skill in the art would have been motivated and been reasonably assured of success in having produced a fusion protein comprising a scfv-cell membrane penetrating transport peptide based on the combined disclosures of Zhao as evidenced by Pavlinkova in view of Toftgard. All of the references appreciate and expressly teach the utility of scfv antibodies. Thus in order to visualize an intracellular antigen such as GLI-1 and GLI-3 as taught by Toftgard or the intracellular antigen of Zhao, the ordinary artisan would have been motivated to have modified an antibody into a scfv not only to decrease the size, but to include a cell membrane permeating peptide such as taught by Zhao in order to facilitate or increase cellular uptake of the antibody into a cell in vitro. In order to detect or visualize an intracellular antigen that was otherwise not accessible to the antibody without permeabilizing the cell itself, one would have been motivated to have engineered a fusion protein where Toftgard and Pavlinkova provided the methods for making fusion constructs and more especially Pavlinkova's teaching of scfvs, to include a cell penetrating peptide based on Zhao. The ordinary artisan would have been motivated at the time of the invention to engineer the cell penetrating peptide to the scfv so that whole cells could be examined in vitro without affecting cell structure or viability (see Zhao at p. 138, Col. 1, ¶1). The ordinary artisan would have been motivated in producing the fusion protein for a diagnostic visualization of intracellular antigen expression in screening cells in vitro and where the fusion protein was formulated into a pharmaceutical composition compatible for administration to living cell in vitro. The ordinary artisan would have been reasonably assured of success in having produced or used the fusion protein for limited applications in vitro because the methods and materials for scfvs and cell penetrating peptides were already available based on the combined disclosures of the cited references, the construction of fusion proteins was already well known based on the combined disclosures of Toftgard and Pavlinkova, and producing a scfv by introduction of a peptide in order to facilitate cellular uptake of the antibody had already been accomplished by Zhao as evidenced by Pavlinkova. For all of the foregoing reasons, the claimed fusion protein was prima facie obvious over Zhao as evidenced by Pavlinkova and Toftgard.

Applicants' allegations on pp. 16 and 17 of the Response of 11/21/08 and the extrinsic experimental evidence provided in Exhibit A have been considered but are not found persuasive. Applicants allege 'there are no teachings of the scFv-part of an

antibody. Neither Zhao et al., nor Toftgard provide any information on how a scFv peptide behaves when linked to a penetrating transport peptide within a cell"; and fusion proteins are unpredictable in activity and this depends on where the cell penetrating transport peptide is fused with respect to the GLI protein based on the extrinsic experimental data.

Response to Arguments

Contrary to Applicants initial assertion, both Zhao as evidenced by Pavlinkova and Toftgard explicitly teach recombinant fusion proteins comprising a recombinant scFv antibody where Toftgard further teaches linking these antibody fragments by recombinant technology to other protein molecules. Zhao teaches cellular uptake for a Mab conjugated with a cell penetrating peptide, and as evidenced by Pavlinkova, insertion of small molecules into a scFv antibody can be accomplished by cross-linking chemistry (see p. 145, Col. 1 of Zhao referencing Pavlinkova). The skilled artisan would recognize that a scFv is itself a recombinant protein generated by recombinant technology from a parent antibody (see p. 3, lines 2-10 and pp. 8-9 of the specification). Thus the instant claimed "recombinant fusion protein" comprises a recombinant "scFv-part of an antibody." The claims do not distinguish which portion of the fusion protein is recombinant. The claims do not distinguish the recombinant scfv portion of the protein being conjugated or recombinant fused to a cell penetrating transport peptide.

The ordinary artisan reviewing the extrinsic data in Exhibit A comparing the scFv anti-GLi3 antibody (5E1) having a C-terminal fusion to transportan (5E1-Tr), the 5E1

antibody alone and the 5E1 antibody chemically linked to Trp 10 (5E1 + TP10) could reasonably conclude that:

a) full length transportan fused to the C-terminus of the 5E1 scFv does not mediate cell uptake into Cos-7 cells;

b) transportan 10 chemically linked to 5E1 scfv mediates cell uptake into Cos-7 cells;

c) it is not clear if transportan 10 fused to the C-terminus of 5E1scfv would mediate uptake into Cos-7 cells;

d) it is not clear if transportan fused to the N-terminus of 5E1 scfv would mediate uptake into Cos-7 cells; and

e) it is not clear where transportan 10 binds to the 5E1 scfv under chemical linkage.

Rather than considering the generation of fusion proteins unpredictable as alleged by Applicants, the ordinary artisan could only conclude these data are inconclusive because of the lack of unmatched controls and the number of questions that are raised rather than answered.

Additionally, the submission of these new data as an exhibit with the actual Response absent any attestation to the facts by the actual inventors is not compliant under 37 CFR 1.132. 37 CFR 1.132 states in part: “when any claim for an application is rejected to…, any evidence submitted to traverse the rejection…on a basis not otherwise provided for must be by way of an oath or declaration under this section.” The purpose of an a 1.132 declaration is to provide a means for submitting evidence to

overcome a rejection, and the kind of evidence in the instant case does not fall under an exception.

This rejection is maintained.

14. The rejection of Claims 19-23, 26, 31 and 33 under 35 U.S.C. 103(a) as being unpatentable over Zhao et al. (J. Method. Immunol. 254:137-145 (2001); cited in the PTO 892 form of 2/12/08) as evidenced by Pavlinkova et al. (J. Immunol. Methods 201:77-88 (1997)) in view of in view of Toftgard (WO 01/12655; cited in the PTO 892 form of 2/12/08) as applied to claims 19, 20, 23 and 26 above, and further in view of Rothbard (WO/ 98/52614; cited in the PTO 892 form of 2/12/08) and Lindgren et al. (Trends in Pharm. Sciences 21:99-103 (3/2000); cited in the PTO 892 form of 2/12/08) is maintained.

For purposes of review, the rejection was set forth in the Office Action of 5/21/08 as follows:

"The claimed fusion proteins were prime facie obvious at the time of the invention over Zhao as evidenced by Pavlinkova in view of Toftgard and further in view of Rothbard and Lindgren.

The interpretation of Zhao as evidenced by Pavlinkova in view of Toftgard is discussed above under section 14. Zhao appreciates intracellular targeting of antibody scfv's using membrane penetrating peptides conjugated to scfv, and Toftgard and Pavlinkova appreciate scfvs and making fusion protein constructs, but do no expressly teach the peptides for transportan, transportan 10 or Arg9, whereas do Rothbard and Lindgren.

Rothbard teaches poly -Arg peptides of from 4-9 residues (p. 7) or from 6 to 25 subunits (p. 10) for use as cell membrane transport peptides of selected agents across any number of biological membranes (p. 6, lines 1-7). Rothbard explicitly teaches delivering antibodies or antibody fragments such as scfv to the cytosol by attaching the transport polymers to the scfv, and that "the principle obstacle to wide application of this technology has been efficiency of uptake into infected cells" (p. 25, lines 10-21).

Lindgren teaches cell penetrating peptides for transportan (Table 1, Table 2, p. 99, Col. 1), and the use of this and other peptides for cellular delivery of drugs or research tools (p. 102, Col. 2).

One of ordinary skill in the art would have been motivated and been reasonably assured of success in having produced a fusion protein comprising a scfv-cell membrane penetrating transport peptide based on the combined disclosures of Zhao as evidenced by Pavlinkova in view of Toftgard and further in view of Rothbard and Lindgren. Zhao as evidenced by Pavlinkova in view of Toftgard provide the motivation to produce fusion proteins comprising a sfv and a cell membrane penetrating peptide to facilitate transport of the scfv into a viable cell in vitro for whole cell visualization of the targeted antigen. One skilled in the art would have found more than sufficient motivation to substitute different cell membrane penetrating peptides in the fusion protein comprising the scfv based on Zhao and Rothbard because each explicitly teach the advantages of small antibody forms like scfv and transport peptides which could be used to facilitate cell entry of the scfv. Rothbard and Lindgren teach different structural

classes of transport peptides encompassing transportan and Arg 9 and provide the explicit motivation to use the peptides to convey molecules across cell membranes that would otherwise be impermeable. The ordinary artisan would have been reasonably assured of success in having produced the fusion proteins and used them to visualize a target antigen in vitro in whole, living cells because as between all of the references all of the methods and reagents were already available and had been shown to work in related molecules for similar purposes. For all of the foregoing reasons, the claimed fusion protein was prima facie obvious over Zhao as evidenced by Pavlinkova and Toftgard in view of Rothbard and Lindgren.

Applicants allegations on p. 16 and 17 of the Response of 11/21/08 and the extrinsic experimental evidence provided in Exhibit A have been considered but are not found persuasive. Applicants allege ‘there are no teachings of the scFv-part of an antibody. Neither Zhao et al., nor Toftgard provide any information on how a scFv peptide behaves when linked to a penetrating transport peptide within a cell”; “Lindgren et al. teach intracellular delivery of cell penetrating peptides, in particular, the properties of Transportan as a transporter peptide, however, none of the references teach the claimed fusion protein (as now claimed) or the substitutions of known sequences for another to obtain predictable results yielding the claimed fusion proteins”; and fusion proteins are unpredictable in activity and this depends on where the cell penetrating transport peptide is fused with respect to the GLI protein based on the extrinsic experimental data.

Response to Arguments

See the examiners comments under section 13 above as they apply here regarding the primary references, the inconclusiveness of the extrinsic evidence and Applicants’ non-compliance under 37 CFR 1.132 for submission of these data.

15. The rejection of Claims 19, 21-23, 26, 31 and 33 under 35 U.S.C. 103(a) as being unpatentable over Rothbard (WO 98/52614; cited in the PTO 892 form of 2/12/08) in view of Lindgren et al. (Trends in Pharm. Sciences 21:99-103 (3/2000); cited in the PTO 892 form of 2/12/08) is maintained.

For purposes of review, the rejection was set forth in the Office Action of 5/21/08 as follows:

"The claimed fusion proteins were prime facie obvious at the time of the invention over Rothbard in view Lindgren.

Rothbard teaches poly -Arg peptides of from 4-9 residues (p. 7) or from 6 to 25 subunits (p. 10) for use as cell membrane transport peptides of selected agents across any number of biological membranes (p. 6, lines 1-7). Rothbard explicitly teaches delivering antibodies or antibody fragments such as scfv to the cytosol by attaching the transport polymers to the scfv, and that "the principle obstacle to wide application of this technology has been efficiency of uptake into infected cells" (p. 25, lines 10-21). Rothbard explicitly teaches fusion polypeptides comprising the polypeptide of interest and the transport peptide (p. 15, lines 15-20; p. 25, lines 29-31). Rothbard teaches that targets can be visualized with the fusion proteins (Example 4) and using the fusion proteins in pharmaceutical compositions (p. 7, lines 9-12). Rothbard explicitly teaches transport peptides fused to scfv but does not disclose transportan as a species whereas does Lindgren.

Lindgren teaches cell penetrating peptides for transportan (Table 1, Table 2, p. 99, Col. 1), and the use of this and other peptides for cellular delivery of drugs or research tools (p. 102, Col. 2).

One of ordinary skill in the art would have been motivated and been reasonably assured of success in having produced a fusion protein comprising a scfv-cell membrane penetrating transport peptide at the time of the invention based on the combined disclosures of Rothbard in view Lindgren. One skilled in the art would have been motivated to produce fusion proteins comprising a sfv and a cell membrane penetrating peptide to facilitate transport of the scfv into a viable cell in vitro for whole cell visualization of the targeted antigen based on the disclosure or Rothbard alone. One skilled in the art would have found more than sufficient motivation to substitute different cell membrane penetrating peptides in the fusion protein comprising the scfv based on Rothbard because Rothbard explicitly teaches the advantages of small antibody forms like scfv and transport peptides such as Arg 9 peptides which could be used to facilitate cell entry of the scfv, and Lindgren teaches different structural classes of transport peptides encompassing transportan to deliver agents into cells that would otherwise be impermeable. The ordinary artisan would have been reasonably assured of success in having produced the fusion proteins and used them to visualize a target antigen in vitro in whole, living cells because as between all of the references, all of the methods and reagents were already available and had been shown to work in related molecules for similar purposes. For all of the foregoing reasons, the claimed fusion protein was prima facie obvious over Rothbard and Lindgren.

Applicants allegations on p. 16 and 17 of the Response of 11/21/08 and the extrinsic experimental evidence provided in Exhibit A have been considered but are not found persuasive.

<u>Response to Arguments</u>

Rothbard teaches on p. 13, lines 15-20:

"B. Fusion Polypeptides

Transport peptide polymers of the invention can be attached to biologically active polypeptide agents by recombinant means by constructing vectors for fusion proteins comprising the polypeptide of interest and the transport peptide, according to methods well known in the art. Generally, the transport peptide component will be attached at the C-terminus or N-terminus of the polypeptide of interest, optionally via a short peptide linker", which when taken in view of Rothbards further disclosure for scFv and cell membrane transport peptides, is considered to read on and therefore anticipate or ender obvious at least generic claim 19.

The skilled artisan would recognize that a scFv is itself a recombinant protein generated by recombinant technology from a parent antibody (see p. 3, lines 2-10 and pp. 8-9 of the specification). Thus the instant claimed "recombinant fusion protein" comprises a recombinant "scFv-part of an antibody." The claims do not distinguish which portion of the fusion protein is recombinant. The claims do not distinguish the recombinant scfv portion of the protein being conjugated or recombinant fused to a cell penetrating transport peptide.

The ordinary artisan reviewing the extrinsic data in Exhibit A comparing the scFv anti-GLi3 antibody (5E1) having a C-terminal fusion to transportan (5E1-Tr), the 5E1 antibody alone and the 5E1 antibody chemically linked to Trp 10 (5E1 + TP10) could reasonably conclude that:

a) full length transportan fused to the C-terminus of the 5E1 scFv does not mediate cell uptake into Cos-7 cells;

b) transportan 10 chemically linked to 5E1 scfv mediates cell uptake into Cos-7 cells;

c) it is not clear if transportan 10 fused to the C-terminus of 5E1scfv would mediate uptake into Cos-7 cells;

d) it is not clear if transportan fused to the N-terminus of 5E1 scfv would mediate uptake into Cos-7 cells; and

e) it is not clear where transportan 10 binds to the 5E1 scfv under chemical linkage.

Rather than considering the generation of fusion proteins unpredictable as alleged by Applicants, the ordinary artisan could reasonably find these data are inconclusive because of the lack of unmatched controls and the number of questions that are raised rather than answered.

Additionally, the submission of these new data as an exhibit with the actual Response absent any attestation to the facts by the actual inventors is not compliant under 37 CFR 1.132. 37 CFR 1.132 states in part: “when any claim for an application is rejected to…, any evidence submitted to traverse the rejection…on a basis not otherwise provided for must be by way of an oath or declaration under this section.” The purpose of an a 1.132 declaration is to provide a means for submitting evidence to overcome a rejection, and the kind of evidence in the instant case does not fall under an exception to this rule.

This rejection is maintained.

16. The rejection of Claims 19-23, 26, 31 and 33 under 35 U.S.C. 103(a) as being unpatentable over Rothbard (WO 98/52614; cited in the PTO 892 form of 2/12/08) in view of Lindgren et al. (Trends in Pharm. Sciences 21:99-103 (3/2000); cited in the PTO 892 form of 2/12/08) as applied to claims 19, 21, 23 and 26 above, and further in view of Toftgard (WO 01/12655; cited in the PTO 892 form of 2/12/08) is maintained.

For purposes of review, the rejection was set forth in the Office Action of 5/21/08 as follows:

“The claimed fusion proteins were prime facie obvious at the time of the invention over Rothbard in view Lindgren and Toftgard.

The interpretation of Rothbard in view Lindgren is discussed above under section 17. Rothbard appreciates scfv directed against many different target antigens and using the scfvs in the form of a fusion protein with a transport peptide to mediate or facilitate uptake but does not disclose the scfv recognizing GLI proteins such as GLI-1 and GLI-3, whereas does Toftgard.

Toftgard discloses the GLI-1 protein (see entire document) and the GLI-3 protein (pp. 3, 24 and 36) and making antibodies against these intracellular antigens (p. 12, lines 1-14). Included amongst the antibodies are single chain antibodies, and pharmaceutical compositions comprising the antibodies and carriers (p. 3, line 25; p. 12, lines 16-20; p. 13, lines 10-15). Toftgard teaches the technology for making protein fusion constructs in general (p. 28, lines 15-16).

One of ordinary skill in the art would have been motivated and been reasonably assured of success in having produced a fusion protein comprising a scfv-cell membrane penetrating transport peptide at the time of the invention based on the combined disclosures of Rothbard and Lindgren in view of Toftgard. Rothbard and Toftgard appreciate and expressly teach the utility of scfv antibodies. Thus in order to visualize an intracellular antigen such as GLI-1 and GLI-3 as taught by Toftgard or an intracellular antigen of Rothbard, the ordinary artisan would have been motivated to have modified an antibody into a scfv not only to decrease the size, but to include a cell membrane permeating peptide such as taught by Rothbard and Lindgren in order to facilitate or increase cellular uptake of the antibody into a cell in vitro. In order to detect or visualize an intracellular antigen that was otherwise not accessible to the antibody without permeabilizing the cell itself, one would have been motivated to have engineered a fusion protein where Rothbard abd Toftgard provided the methods for making fusion constructs and more especially Rothbard’s ’s teaching of scfvs, to include a cell penetrating peptide including Arg 9 and the peptides of Lindgren. The ordinary artisan would have been motivated at the time of the invention to engineer the cell penetrating peptide to the scfv so that whole cells could be examined in vitro without affecting cell structure or viability. The ordinary artisan would have been motivated in producing the fusion protein for a diagnostic visualization of intracellular antigen expression in screening cells in vitro and where the fusion protein was formulated into a pharmaceutical composition compatible for administration to living cell in vitro. The ordinary artisan would have been reasonably assured of success in having produced or used the fusion protein for limited applications in vitro because the methods and materials for scfvs and cell penetrating peptides were already available based on the combined disclosures of the cited references, the construction of fusion proteins was already well known based on the combined disclosures of Rothbard and Toftgard, and producing a scfv by introduction of a peptide in order to facilitate cellular uptake of the antibody had already been accomplished by Rothbard. For all of the foregoing reasons, the claimed fusion protein was prima facie obvious over Rothbard, Lindgren and Toftgard.

Applicants allegations on p. 16 and 17 of the Response of 11/21/08 and the extrinsic experimental evidence provided in Exhibit A have been considered but are not found persuasive.

Response to Arguments

See the examiners comments under section 15 above as they apply here regarding the primary references, the inconclusiveness of the extrinsic evidence and Applicants' non-compliance under 37 CFR 1.132 for submission of these data.

This rejection is maintained.

Objections Maintained

Specification

17. The objection to the legend to Figure 2 as having the same description for panels 2A and 2C and the same description for panels 2B and 2D is maintained. Applicants are requested to compare the language between 2A and 2C, and 2C and 2D, which appears to be duplicative. Clarification is requested.

New Grounds for Rejection

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

18. Claim 23 is rejected under 35 U.S.C. 101 because the claimed recitation of a use, i.e., "medical use", without setting forth any steps involved in the process, results in

an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example Ex parte Dunki, 153 USPQ 678 (Bd. App. 1967) and Clinical Products Ltd. v. Brenner, 255 F Supp. 131,149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

19. Claims 19-23, 26 and 31-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rothbard (WO 98/52614; cited in the PTO 892 form of 2/12/08) in view of Toftgard (WO 01/12655; cited in the PTO 892 form of 2/12/08) and further in view of Lindgren et al. (Trends in Pharm. Sciences 21:99-103 (3/2000); cited in the PTO 892 form of 2/12/08) and Soomets et al. (Biochem. Biophys. Acta 1467:165-176 (2000) cited I the IDS of 11/21/08).

Claim 19 is interpreted as being drawn to any recombinant fusion protein comprising any scfv and any cell-penetrating transport peptide where each of these elements is “at least” what comprises a fusion protein. The structure of the protein and the elements linking the two moieties are interpreted as being unlimited given the comprising language. Claims 20 is interpreted as being drawn to

Claim 20 is interpreted as being drawn to an anti- GLI protein scfv, where the protein is GLI-1 or GLI-3, and any cell-penetrating transport peptide where each of these elements is “at least” what comprises a fusion protein.

Claim 21 is interpreted as being drawn to the fusion protein of Claim 19 where the cell transport peptide is Transportan, Transportan 10 or Arg 9.

Claim 23 is interpreted as being drawn to using the fusion protein of Claim 19 to visualize an intracellular antigen for diagnosing, for example.

Claim 26 is interpreted as a pharmaceutical composition comprising the fusion protein of Claim 19.

Claims 31-33 are drawn to the fusion protein of Claim 19 where the cell-penetrating transport peptide is Transportan (Claim 31), Transportan 10 (Claim 32) or Arg 9 (Claim 33).

The claimed recombinant fusion proteins were prime facie obvious at the time of the invention over Rothbard, Toftgard, Lindgren and Soomets.

Rothbard teaches poly -Arg peptides of from 4-9 residues (p. 7) or from 6 to 25 subunits (p. 10) for use as cell membrane transport peptides of selected agents across any number of biological membranes (p. 6, lines 1-7). Rothbard explicitly teaches

delivering antibodies or antibody fragments such as scfv to the cytosol by attaching the transport polymers to the scfv, and that “the principle obstacle to wide application of this technology has been efficiency of uptake into infected cells” (p. 25, lines 10-21). Rothbard explicitly teaches fusion polypeptides comprising a polypeptide of interest and the transport peptide (p. 15, lines 15-20; p. 25, lines 29-31). Rothbard teaches that targets can be visualized with the fusion proteins (Example 4) and using the fusion proteins in pharmaceutical compositions (p. 7, lines 9-12).

Toftgard discloses the GLI-1 protein (see entire document) and the GLI-3 protein (pp. 3, 24 and 36) and making antibodies against these intracellular antigens (p. 12, lines 1-14). Included amongst the antibodies are single chain antibodies, and pharmaceutical compositions comprising the antibodies and carriers (p. 3, line 25; p. 12, lines 16-20; p. 13, lines 10-15). Toftgard teaches the technology for making protein fusion constructs in general (p. 28, lines 15-16).

Lindgren teaches cell penetrating peptides for transportan (Table 1, Table 2; p. 101, Col. 1, ¶4-5), and the use of this and other peptides for cellular delivery of drugs or research tools (p. 102, Col. 2). Lindgren teaches:

“After a l min incubation at 37°C, transportan is found m the plasma membrane and its redistribution to the nuclear envelope and other intracellular membranes follows rapidly. Cellular uptake is not blocked by unlabelled transportan or galanin, or by incubation of the cells at 4°C or in hyperosmolar sucrose solution. Uptake kinetics exhibit a rapid saturation of the cells, followed by a slow leakage of the radio-iodinated peptide into the medium2s. Furthermore, transportan is enriched in cells, and at saturation the intracellular concentration is at least twofold higher than the extracellular concentration2s. At concentrations ≤ 20 μM, transportan shows no apparent toxicity” (p. 101, Col. 1, ¶5).

Soomets teaches generating peptide mutants based on the wild-type transportan to generate transportan 10 as shown in Table I on p. 691. Transportan 10 internalized to a comparable degree with tranpsortan at different temperatures, The peptide was detected in the cytoplasm and nucleus of Bowes cells, accumulating mainly in the intracellular membranous structures and nuclear envelope (p. 170, Col. 1 to Col. 2; Figure 1). Soomets teaches TP and TP10 penetrate into different cells in rapid and efficient way, the penetration is energy independent and not receptor-mediated.

Soomets teaches:

"…we have synthesized several shorter TP analogies that retain the efficient cell penetration property of the parent compound. One of these, TP10, does not modulate the basal GTPase activity even at bery high concentrations nor is it recognized by galanin receptors. These features make TP10 a promising candidate for a new generation of transporter peptide with significantly less potential side effects" (p. 175, Col. 2).

One of ordinary skill in the art would have been motivated and been reasonably assured of success in having produced a fusion protein comprising a scfv-cell membrane penetrating transport peptide at the time of the invention based on the combined disclosures of Rothbard, Toftgard, Lindgren and Soomets. Rothbard and Toftgard appreciate and expressly teach the utility of scfv antibody size in penetrating tissues. Thus in order to visualize an intracellular antigen such as GLI-1 and GLI-3 as taught by Toftgard or an intracellular antigen of Rothbard, the ordinary artisan would have been motivated to have modified an antibody into a scfv not only to decrease the size, but to include a cell membrane permeating peptide such as taught by Rothbard and Lindgren and Soomets in order to facilitate much less increase cellular uptake of

the scfv antibody into a cell in vitro. In order to detect or visualize an intracellular antigen such as GLI-1 or GLI-3 as taught by Toftgard that was otherwise not accessible to an antibody without permeabilizing the cell itself, one would have been motivated to have engineered a fusion protein where Rothbard and Toftgard provided the methods for making fusion constructs for scfv and more especially Rothbard's 's teaching of scfvs, to include a cell penetrating peptide including Arg 9 and further in view of the peptides of Lindgren and Soomets. The ordinary artisan would have been motivated at the time of the invention to engineer the cell penetrating peptide to the scfv so that whole cells could be examined in vitro without affecting cell structure or viability. The ordinary artisan would have been motivated in producing the fusion protein for a diagnostic visualization of intracellular antigen expression in screening cells in vitro and where the fusion protein was formulated into a pharmaceutical composition compatible for administration to living cell in vitro to visualize GLI-1 and GLI-3. The ordinary artisan would have been reasonably assured of success in having produced or used the fusion protein for limited applications in vitro because the methods and materials for scfvs and cell penetrating peptides were already available based on the combined disclosures of the cited references, the construction of fusion proteins was already well known based on the combined disclosures of Rothbard and Toftgard, producing a scfv by introduction of a peptide in order to facilitate cellular uptake of the antibody had already been accomplished by Rothbard, and cell-membrane penetrating peptides were already known to be more effective than others based on Rothbard, Lingard and Soomets. For

all of the foregoing reasons, the claimed fusion protein was prima facie obvious over Rothbard, Lindgren, Toftgard and Soomets.

Conclusion

20. No claims are allowed.

21. Any inquiry concerning this communication or earlier communications from the examiner should be directed to LYNN BRISTOL whose telephone number is (571)272-6883. The examiner can normally be reached on 8:00-4:30, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Lynn Bristol/

Examiner, Art Unit 1643
Partial Signatory Authority